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09/492,213	01/27/2000	Gerard J Gundling	6416.US.P1	9588

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EXAMINER
SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 03/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/492,213	GUNDLING ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,8 and 12-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,8 and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 4, 7, 8, 12, 13, and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co.*,

> *Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The Quantity of Experimentation Necessary and The Amount of Direction or Guidance Provided

3. The quantity of experimentation required to enable a skilled artisan to practice the full scope of the claimed invention is immense. As amended, the claims more clearly recite that one is to render incapable of use in any amplification reaction, the presence of carry-over or contaminating nucleic acids through the application of an electric current of undefined duration and strength.

4. The specification does not provide any examples.

5. The specification does, however, provide motivation for others to determine how the claimed invention is to be practiced. In support of this position, attention is directed to page 57, lines 4-10, where it is stated:

> It is believed that that signal may elute or lyse a nucleic acid. Alternatively, that signal may attenuate, change or otherwise effect biological and/or bio-molecular elements, such as a nucleic acid and the like, in the fluid 95 such that those elements have a reduced ability to be amplified or detected in a PCR reaction.

6. While it is not a requirement that applicant set forth each and every possible set of conditions that could be envisioned so as to satisfy the requirements for enablement under 35 USC 112, first paragraph, the specification must set forth at least some of those conditions as it is now well settled that to not disclose the starting materials and the reaction conditions to be used in practicing the claimed invention unfairly shifts the burden of enablement from that of applicant to the public. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

" '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

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"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
"It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

The Presence or Absence of Working Examples

7. The specification provides no working examples.

The Nature of the Invention

8. The invention relates to the world of biochemistry and electrical conductance. More specifically, the invention relates to the separation of one population of nucleic acids from another population of nucleic acids whilst in a common container, by the application of an electric current when the first and second nucleic acids may have identical. Sequences.

The State of the Prior Art

9. The aspect of contaminants in various nucleic acid amplification assays is well known in the art as is the effect of contaminants in nucleic acid amplification assays have been approached through the use of chemicals such as uracil-N-glycosylase (UDG; US Patent 5,536,649) as well as the encasement of PCR reactants in a wax matrix (US Patent 5,576,197). The state of the prior art is wholly undeveloped as it relates to the application of electric currents to various samples in an effort to reduce or eliminate any contaminating material, e.g., nucleic acids, as well as any other ligand and its receptor(s).

The Relative Skill of Those in the Art

10. The relative skill of those in the art most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

The predictability or unpredictability of the art

11. The predictability of the art is low as it deals with matters of chemistry and cellular physiology- two art areas that have been recognized by the court as being notoriously unpredictable.[1]

The breadth of the claims

12. Claims 1, 4, 12, and 13 have sufficient breadth of scope so to encompass the binding of a first target nucleic acid when the first target nucleic acid is the subject of an amplification reaction. While agreement is reached in that the first nucleic acid could possibly contaminate an amplification reaction used to amplify a second nucleic acid target, the method makes no distinction between a first nucleic acid sample that is to be amplified and one attempting to amplify a second nucleic acid.

13. Additionally, the method of claim 1, for example, does not require that the electrical current be continued during any amplification reaction. Seemingly, the termination of the electrical current would result in the liberation of any freed first nucleic acid sample such that it could be amplified in the second reaction. Conversely, if the electrical current was allowed to remain on, it stands to reason that the current that served to immobilize the first nucleic cid would also serve to immobilize the second nucleic acid.

14. In the case of claim 12 it is required that a current be passed, though not terminated at any point, whereby a potentially contaminating first nucleic acid is fragmented by the application

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[1] As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving

of an electrical current. The level of fragmentation is not clearly defined. As presently worded, it stands to reason that the fragmentation of a previously intact nucleic cid target into that of oligonucleotides could very easily result in the generation of a plethora of unintended primers that could in term amplify unintended regions of the second nucleic cid sample, thereby giving the impression of contamination or at the very least, non-specific amplification whereby a multitude of amplicons of varying sizes and sequences could be synthesized.

15. Claim 14 requires that the target nucleic acid be immobilized to a solid support, e.g., a microparticle, and that it is subjected to an electrical field of sufficient magnitude that it will be "eluted" from the particle. The specification does not fully enable this aspect of the invention. While one may well apply an electrical field so to cause the nucleic acid present therein to migrate toward one of the terminals, the particle is not required to be of any particular size and as such, the use of certain particles may well result in the co-migration of the tethered nucleic acid complex, not the "elution" of the nucleic acid from such a particle.

Response to arguments

16. At page 4 of the response filed 11 November 2002 (response) applicant asserts that the rejection should be withdrawn for "[w]hile use of the treated analyzer to analyze a second sample is a natural use of the treated analyzer, applicants do not understand why additional steps need be recited when these steps are not essential to the novelty of non-obviousness of the present invention."

17. The above traversal has been fully considered and has not been found persuasive towards the rejection. It is noted with particularity that the claimed method has been rejected under 35

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unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously

USC 112, first paragraph, as it relates to enablement. The claims, as of the last Office action, had not been rejected under either 35 USC 102, as it relates to novelty, nor under 35 USC 103(a) as it relates to obviousness. In short, novelty and non-obviousness have nothing to do with enabling the claimed invention.

18. The claimed method fairly encompasses subsequent uses of the device. And that the assay could be performed an infinite number of occasions. Additionally, the sample that is contaminated with nucleic acid could also contain a second or mixture of other target nucleic acids, some of which could be identical to the "contaminating" nucleic acid. The specification does not set forth a reproducible method whereby a "contaminating" nucleic acid could be selectively removed from an analyzer when a target nucleic acid is also present simultaneously, be the target and contaminating nucleic acids identical in nucleotide composition or different.

19. It is further noted that no limitation has been placed against the type of analyzer that is to be used. Accordingly, the "analyzer" could be virtually any type of analyzer, e.g., electrophoresis, quantitative, qualitative, sequencing, etc.

20. While applicant is not required to provide examples in their disclosure, the disclosure must still fully enable the scope of the claimed invention. Such has not happened here.

21. At page 5, second full paragraph, applicant asserts that they do not understand how their invention works, but that it does. Argument is also advanced that "While in most embodiments applicants might advise turning off the current, this is not a known limitation of the process."

22. While applicant may not be aware of inoperable embodiments, such lack of knowledge in and of its self is not dispositive of the requirements of applicant fully enabling the claimed

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varies inversely with the degree of unpredictability of the factors involved.

invention. As presently worded, the current may be maintained throughout the assay. It stands to reason that if the "contaminating" nucleic acid can be fragmented by the electrical current, then the target nucleic acid can also be fragmented whether the "second sample" / "second nucleic acid" and "contaminating" / "first nucleic acid" are the same or different. Also, the claimed method encompasses the selective fragmenting of a heterogeneous mixture of nucleic acids where multiplex PCR assays may be conducted. The specification fails to set forth a repeatable procedure whereby such selective fragmentation can be performed.

23. At page 5, last paragraph, applicant asserts that they have conducted experiments and have found "that the fragmentation of contaminating nucleic acids does indeed attenuate the signal generated by the contaminates." It is noted, however, that no data has been provided which would support these conclusions, and especially where selective fragmentation of one nucleic acid over that of another, when they are both in sample, and where the current is maintained throughout.

24. At page 6, argument is advanced that applicant is unaware of non-enabling embodiments. As indicated above, applicant's lack of being aware of non-enabling embodiments is not dispositive where as here the Office has fairly raised questions of enablement. Seemingly, in order to meet the test established by applicant in that they are wholly unaware of any non-enabling disclosure, all one needs to do is NOT perform any analysis of any embodiment of the claimed invention. A review of the disclosure fails to find any example and the disclosure more generally fails to set forth reaction conditions whereby the full scope of the claimed invention can be practiced. Such non-disclosure of conditions under which the claimed method is to be

practiced has been held to constitute non-enablement. *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001.

25. For the above reasons, and in the absence of convincing evidence to the contrary, the rejection is maintained.

Claim Rejections - 35 USC § 102

26. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

27. Claims 1, 12, and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoefer et al. (WO 87/00635).

28. Hoefer et al., disclose a method whereby a nucleic acid analyzer (an electrophoretic device) is used to separate various fragments of DNA by the application of an electrical current.

29. It is noted with particularity that the recited "nucleic acid analyzer" is not defined as being capable of performing any specific type f analysis and as such, the claims have been interpreted as encompassing virtually an such analyzer, including electrophoretic devices. Also, while the claims make reference to possible amplification of the nucleic acid, no actual amplification is performed. Accordingly, the electrophoretic device is considered to meet a requirement of the recited "nucleic acid analyzer" and the application of electrical current of

sufficient strength and duration to effect separation of DNA fragments from other components meets the requirement of having two electrodes adjacent to the nucleic acid.

30. Claims 1, 4, 12-14 and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Northrup et al. (WO 99/47255 A1)

31. Northrup et al., disclose a unitary device whereby electrodes are used to move a sample into a reaction chamber as well as out of the chamber. Page 6, first full paragraph, states that one or more electrodes may be embedded in one or more regions of the device. Such a teaching fairly anticipates the aspect of having electrodes adjacent to the nucleic acid. Page 7, last paragraph, discloses having electrical connections for applying voltage difference between the electrodes. Element **154** is defined as being a reaction chamber that can be used in an amplification reaction. Page 13, first full paragraph, teaches of channels that can be used to add or remove fluids. Such teachings are considered to meet the limitation of a pipettor being used to remove fluids. Page 8, last paragraph, discloses using immobilized reagents, e.g., immobilized polynucleotide probes.

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

34. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

35. Claims 1, 4, and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Northrup et al., in view of Zander et al.

36. See above for the basis f the rejection as it relates to the disclosure of Northrup et al.

37. Northrup et al., does not disclose using microparticles.

38. Zander et al., discloses using microparticles or beads for the immobilization or capture of polynucleotides.

39. It would have been obvious to one of ordinary skill in the art at the time that the invention was made to have modified the method of Northrup et al., whereby microparticles were used for

the immobilization of polynucleotides as such provides an enhancement of surface area, thereby allowing for greater binding capacity n a limited area.

40. In view of the detailed teachings of the prior art and the benefits of using microparticles, the ordinary artisan would have been amply motivated to effect the modification and would have also had a most reasonably expectation of success.

Conclusion

41. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

42. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

43. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
March 13, 2003